

As per

wherein,

R^1 and R^2 , simultaneously or independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R^1 and R^2 together form $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ or $-CH_2-CH_2-CH_2-$, in which the carbons may be substituted with one or a plurality of alkyl groups having 1 to 4 carbons;

A represents a single bond, a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, in which the substituent represents a halogen atom, OH, NO_2 , CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group;

AMENDMENT UNDER 37 C.F.R. § 1.111
U.S. APPLN. 09/743,483

Sub
E represents COOR^3 , SO_3R^3 , CONHR^3 , SO_2NHR^3 , a tetrazole group, a 5-oxo-1,2,4-oxadiazole group or a 5-oxo-1,2,4-thiadiazole group in which R^3 represents a hydrogen atom, or a linear or branched alkyl group having 1 to 6 carbons;

A
G represents a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons that may be interrupted with one or a plurality of O, S, SO_2 , and NR^3 , in which R^3 is as defined above and the substituent represents a halogen atom, OH, NO_2 , CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or 15 branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, or an oxo group;

A
m represents an integer of 0 to 2;

Cont
when m is 0 and A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 3 to 6 carbons, a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, with the proviso that J does not represent 2,5-dimethylimidazole-4-yl, when G represents $-\text{CH}_2-$;

when m is 0 and A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted

AMENDMENT UNDER 37 C.F.R. § 1.111
U.S. APPLN. 09/743,483

Sub 36
heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, with the proviso that J does not represent unsubstituted, linear or branched alkyl groups having 1 to 6 carbon atoms, when A represents a pyrimidine ring and the position 2 of the pyrimidine ring binds to the methylene adjacent to the S in the formula (1); or

Al Cont
when m is 0 and A is a single bond or when m is 1 or 2, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, in which the substituent represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a substituted or unsubstituted anilide group, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, a COOR³ group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group, with the proviso that J does not represent 2,5-dimethylimidazole-4-yl, when m is 0, A is a single bond, and G represents -CH₂; and further with the proviso that J does not represent unsubstituted, linear or branched alkyl groups having 1 to 6 carbon atoms, when A represents a pyrimidine ring and the position 2 of the pyrimidine ring binds to the methylene adjacent to the S in the formula (1); and

AMENDMENT UNDER 37 C.F.R. § 1.111
U.S. APPLN. 09/743,483

Sub E
X represents CH or a nitrogen atom;
or a medically acceptable salt thereof.

2. (Amended) The thiobenzimidazole compound according to claim 1 wherein, A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

All Cont
3. (Amended) The thiobenzimidazole compound according to claim 1, wherein A is a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

4. (Amended) The thiobenzimidazole compound according to claim 1, wherein m is 1, or a medically acceptable salt thereof.

5. (Amended) The thiobenzimidazole compound according to claim 1, wherein m is 2, or a medically acceptable salt thereof.

6. (Amended) The thiobenzimidazole compound according to claim 1, wherein m is 0, A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons,

and J is a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

7. (Amended) The thiobenzimidazole compound according to claim 1, wherein m is 0, A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, and J is a substituted or unsubstituted aryl group having 6 to 11 carbons or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

8. (Amended) The thiobenzimidazole compound according to claim 1, wherein G is -CH₂-, -CH₂-CH₂-, -CH₂CO-, -CH₂CH₂O-, -CH₂CONH-, -CO-, -SO₂-, -CH₂SO₂-, -CH₂S- or -CH₂CH₂S-, or a medically acceptable salt thereof.

9. (Amended) The thiobenzimidazole compound according to claim 1, wherein R¹ and R² simultaneously represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R¹ and R², independently of each other, represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, a trihalomethyl group, a cyano group, or a hydroxy group, or a

AMENDMENT UNDER 37 C.F.R. § 1.111
U.S. APPLN. 09/743,483

medically acceptable salt thereof.

A11
Cont

10. (Amended) The thiobenzimidazole compound according to claim 1, wherein E represents COOH or a tetrazole group, or a medically acceptable salt thereof.

11. (Amended) The thiobenzimidazole compound according to claim 1, wherein X represents CH, or a medically acceptable salt thereof.

A2

Sub B2

13. (Amended) A pharmaceutical composition which is a preventive and/or therapeutic agent of a disease comprising at least one human chymase inhibitor thiobenzimidazole compound according to any one of claims 1 to 13 or a medically acceptable salt thereof and a pharmaceutically acceptable carrier.

A3

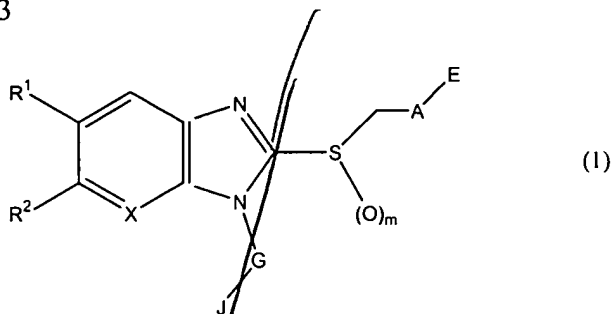
15. (Amended) A pharmaceutical composition according to claim 13, wherein said disease is an inflammatory disease, an allergic disease, a disease of respiratory organs, a disease of circulatory organs, or a disease of bone/cartilage metabolism.

Claims 16 and 17 are added as new claims.

A4

Sub B2

16. (New) A method for inhibiting human chymase comprising administering a biologically effective amount of a pharmaceutical composition comprising a thiobenzimidazole compound as the active ingredient represented by the following formula (I):



wherein, R^1 and R^2 , simultaneously or independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R^1 and R^2 together form $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ or $-CH_2-CH_2-CH_2-$, in which the carbons may be substituted with one or a plurality of alkyl groups having 1 to 4 carbons;

A represents a single bond, a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, in which the substituent represents a halogen atom, OH, NO_2 , CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group;

E represents $COOR^3$, SO_3R^3 , $CONHR^3$, SO_2NHR^3 , a tetrazole group, a 5-oxo-1,2,4-

AMENDMENT UNDER 37 C.F.R. § 1.111
U.S. APPLN. 09/743,483

oxadiazole group or a 5-oxo-1,2,4-thiadiazole group in which R^3 represents a hydrogen atom, or a linear or branched alkyl group having 1 to 6 carbons;

Ad 58
G represents a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons that may be interrupted with one or a plurality of O, S, SO_2 , and NR^3 , in which R^3 is as defined above and the substituent represents a halogen atom, OH, NO_2 , CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or 15 branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, or an oxo group;

Q4
Cont
m represents an integer of 0 to 2;

when m is 0 and A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 3 to 6 carbons, a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, with the proviso that J does not represent 2,5-dimethylimidazole-4-yl, when G represents $-CH_2-$;

when m is 0 and A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen

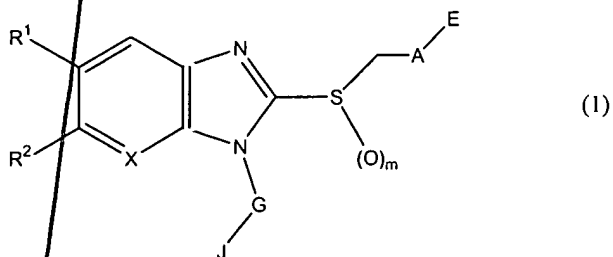
AMENDMENT UNDER 37 C.F.R. § 1.111
U.S. APPLN. 09/743,483

and sulfur atoms on the ring, with the proviso that J does not represent unsubstituted, linear or branched alkyl group having 1 to 6 carbon atoms, when A represents a pyrimidine ring and the position 2 of the pyrimidine ring binds to the methylene adjacent to the S in the formula (1); or when m is 0 and A is a single bond or when m is 1 or 2, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, in which the substituent represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a substituted or unsubstituted anilide group, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, a COOR³ group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group, with the proviso that J does not represent 2,5-dimethylimidazole-4-yl, when m is 0, A is a single bond, and G represents -CH₂; and further with the proviso that J does not represent unsubstituted, linear or branched alkyl group having 1 to 6 carbon atoms, when A represents a pyrimidine ring and the position 2 of the pyrimidine ring binds to the methylene adjacent to the S in the formula (1); and

X represents CH or a nitrogen atom;

or a medically acceptable salt thereof.

17. (New) A method for preventing and/or treating a disease selected from the group consisting of an inflammatory disease, an allergic disease, a disease of the respiratory organs, a disease of circulatory organs, and a disease of bone/cartilage metabolism comprising administering a biologically effective amount of a composition comprising a thiobenzimidazole compound as an active ingredient represented by the following formula (1):



wherein,

R^1 and R^2 , simultaneously or independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R^1 and R^2 together form $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ or $-CH_2-CH_2-CH_2-$, in which the carbons may be substituted with one or a plurality of alkyl groups having 1 to 4 carbons;

A represents a single bond, a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, in which the substituent

AMENDMENT UNDER 37 C.F.R. § 1.111
U.S. APPLN. 09/743,483

2/15/05
represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group;

2/4/05
E represents COOR³, SO₃R³, CONHR³, SO₂NHR³, a tetrazole group, a 5-oxo-1,2,4-oxadiazole group or a 5-oxo-1,2,4-thiadiazole group in which R³ represents a hydrogen atom, or a linear or branched alkyl group having 1 to 6 carbons;

cont
G represents a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons that may be interrupted with one or a plurality of O, S, SO₂, and NR³, in which R³ is as defined above and the substituent represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, or an oxo group;

m represents an integer of 0 to 2;

when m is 0 and A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 3 to 6 carbons, a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, a substituted or unsubstituted

AMENDMENT UNDER 37 C.F.R. § 1.111

U.S. APPLN. 09/743,483

heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, with the proviso that J does not represent 2,5-dimethylimidazole-4-yl, when G represents $-CH_2-$;

when m is 0 and A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, with the proviso that J does not represent unsubstituted, linear or branched alkyl groups having 1 to 6 carbon atoms, when A represents a pyrimidine ring and the position 2 of the pyrimidine ring binds to the methylene adjacent to the S in the formula (1); or

when m is 0 and A is a single bond or when m is 1 or 2, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, in which the substituent represents a halogen atom, OH, NO_2 , CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a substituted or unsubstituted anilide group, a

AMENDMENT UNDER 37 C.F.R. § 1.111
U.S. APPLN. 09/743,483

trialomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, a COOR³ group, or phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group, with the proviso that J does not represent 2,5-dimethylimidazole-4-yl, when m is 0, A is a single bond, and G represents CH_2 ; and further with the proviso that J does not represent unsubstituted, linear or branched alkyl group having 1 to 6 carbon atoms, when A represents a pyrimidine ring and the position 2 of the pyrimidine ring binds to the methylene adjacent to the S in the formula (1); and

X represents CH or a nitrogen atom;
or a medically acceptable salt thereof.